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Original article

Single center experience in Japanese patients with syncope

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ABSTRACT

Background and purpose: The present diagnostic method and features of syncope in Japan are unclear. Implantable loop recorder (ILR) and head-up tilt tests have recently become available for diagnosing syncope. The examination method and rates of diagnosing syncope may vary. This study aimed to clarify the present diagnostic method and features of syncope in a single Japanese medical center.

Methods and results: We retrospectively reviewed the medical records of consecutive patients who were seen at our hospital from January 1, 2009, to December 31, 2012. A total of 547 patients (328 men, 60.4 ± 21.5 years) with syncope were seen at our hospital. Reflex syncope was diagnosed in 29.1% of the cases, orthostatic hypotension in 11.7%, cardiac syncope in 34.0%, and unexplained syncope in 23.9% by initial and early evaluations. The number of patients with situational syncope and orthostatic hypotension that could be diagnosed in the initial evaluation of the first examination was significantly greater than that in subsequent evaluations. Forty-three percent of the unexplained syncope patients received an ILR. The consent rate for ILR implantations in the unexplained syncope patients with a suspected arrhythmia nature was 53.1%. The cumulative ILR diagnostic rates were 47% and 65% at 1 and 2 years after the ILR implantation, respectively. The estimated ILR diagnostic rates were significantly greater than that for conventional test without using an ILR. When patients with unexplained syncope could be diagnosed, the recurrent symptoms were greatly reduced.

Conclusions: Syncope is induced by various causes in Japan. It is important that we understand the characteristics of each syncope cause. The consent rate for implanting an ILR in appropriate unexplained syncope patients is low. We need to educate these patients about the importance of making a diagnosis of syncope.

Introduction

Syncope is defined as a sudden loss of consciousness associated with a loss of postural tone, from which the patient recovers spontaneously. In Western countries, syncope is a common condition accounting for 1–6% of medical admissions and up to 3% of emergency department visits [1]. There are various causes of syncope and the prognosis of syncope differs according to the cause [1,2]. Actually, the prognosis is bad in cardiac syncope patients and good in reflex syncope patients [2]. Cardiovascular physicians are frequently confused about how to diagnosis syncope. Moreover, in clinical practice, the features of Japanese syncope are unclear. Implantable loop recorder (ILR) and head-up tilt test (HUT) have become available for diagnosing syncope in recent years in Japan. ILR is useful for diagnosing unexplained syncope [3–6] and HUT is performed to confirm the diagnosis in suspected reflex syncope patients [7]. The examination method and diagnosis appear to have been improved by those tests. To confirm the facts and features of the diagnosis is of significance for syncope patients in Japan. The syncope guidelines of the European Society of Cardiology (ESC) were revised in 2009 [8], and the Japanese guidelines were made from that. The guidelines state the new risk classification for unexplained syncope patients [8]. According to the guidelines, we retrospectively analyzed the diagnostic methods and causes of the disease in Japanese syncope patients.

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Methods

Patient population

We retrospectively reviewed the medical records of 547 consecutive patients, from the inpatients and outpatients, who consulted the cardiovascular internal medicine department in our hospital for syncope from January 1, 2009 to December 31, 2012. The patients were excluded from the study if they were experiencing typical non-syncopal events, namely other disorders with impairment or loss of consciousness resembling syncope (i.e. transient ischemic attacks, metabolic disorders, epilepsy, intoxication, cataplexy, drop attacks, and psychogenic disorders). In addition, the patients were excluded if they had head trauma without a syncopal episode, or had a prolonged loss of consciousness disorder. The study was approved by the Ethics Committee of Showa University.

Diagnosis criteria

The patients were diagnosed by 2 cardiovascular medicine specialists using the classification and pathophysiology of syncope described in the ESC guidelines [8]. The diagnoses were sorted into three categories: Reflex syncope, syncope due to orthostatic hypotension (OH), and cardiac syncope. Reflex syncope was defined as syncope triggered by pain, micturition or defecation, prolonged standing, stress, or HUT-induced syncope with a prodrome similar to the clinical symptoms. Syncope due to OH included not only general initial, classic, and delayed OH, but also OH together with reflex syncope and postural orthostatic tachycardia syndrome. OH was diagnosed on the basis of an abnormal decrease in the blood pressure upon standing during the active standing test or HUT. Cardiac syncope included arrhythmias, ischemic heart disease, and mechanical causes as represented by aortic valve stenosis and hypertrophic obstructive cardiomyopathy. Arrhythmic causes of syncope were diagnosed on the basis of documented arrhythmic events or positive electrophysiological study (EPS). Ischemic heart disease was diagnosed by the electrocardiogram (ECG) and coronary angiography including an acetylcholine stress test (CAG). Organic cardiac causes of syncope (i.e. aortic valve stenosis, hypertrophic obstructive cardiomyopathy, etc.) were confirmed by echocardiography. Non-syncope was defined as epilepsy, several metabolic disorders (i.e. hyponatremia and hypoglycemia), or vertebrobasilar transient ischemic attacks.

Diagnosis of syncope (initial evaluation, early evaluation, and late evaluation)

We sorted the initial, early, and late evaluations according to the time of the tests for syncope. We defined the initial evaluation as examinations on the day that the patient consulted the medical institution for syncope for the first time. An early evaluation was defined as tests performed within three months after the syncope. We examined and diagnosed the patients during each evaluation period. Nevertheless, we could not diagnose the patients who were diagnosed with unexplained syncope. We followed up the patients in late evaluation.

Initial evaluation (primary evaluation)

We defined the initial evaluation as possible examinations (i.e. detailed history and blood examination, ECG at the time of the consultation, and standing test), and as appropriate, when these syncope patients were examined for the first time.

We diagnosed reflex syncope and OH by a clinical history of syncope or positive active standing test. Cardiac syncope was confirmed from ECG abnormalities causing the syncope (e.g. complete atrioventricular block and ST elevation due to a myocardial infarction, etc.) at the time of the consultation.

Early evaluation (secondary evaluation)

If we could not diagnose the patients with syncope in the initial evaluation, these patients needed a secondary evaluation. An early evaluation was defined as tests performed during the admission for syncope or during outpatient visits within three months after the onset of the syncope. The tests during the early evaluation period included invasive tests such as an EPS, CAG, and the available tests during the outpatient care (e.g. ultrasound cardiography, 24 hours Holter ECG, and HUT).

Reflex syncope and OH were induced and diagnosed using HUT. We diagnosed structural cardiovascular disease using echocardiography, CAG, or contrast-enhanced computed tomography scan. Arrhythmias were diagnosed by positive EPS or documented arrhythmias causing syncope by prolonged ECG or treadmill test.

Late evaluation (tertiary evaluation)

We followed up the unexplained patients who could not be diagnosed in either evaluation. The follow-up period was from January 1, 2009 to July 31, 2013. The unexplained patients were divided using a risk stratification of unexplained syncope. The risk stratification had three categories, low-risk, low-risk for recurrence, and high-risk groups. The high-risk features were defined according to the ESC guidelines (Table 1) [8]. If a patient without any high-risk features had only one, or two or more episodes of syncope, we placed the patient into the low-risk and low-risk for recurrence groups, respectively. We did not perform any further syncope tests in the low-risk patients. We advised the appropriate patients with a suspected arrhythmia nature in the low-risk for recurrence group and high-risk group to receive an ILR. We performed conventional tests for the unexplained syncope patients without indication and agreement of ILR. We compared the diagnostic rates between the patients with an implanted ILR and those in the group undergoing conventional tests. We evaluated the recurrent symptoms after therapy when the unexplained syncope could be diagnosed in the late evaluation.

Table 1
High-risk features of unexplained syncope according to the European Society of Cardiology guidelines [8].

(1) Severe structural or coronary artery disease
1. Heart failure
2. Low LVEF
3. Previous myocardial infarction
(2) Clinical or ECG features suggesting arrhythmic syncope
1. Syncope during exertion or supine
2. Palpitations at the time of syncope
3. Family history of SCD
4. Non-sustained VT
5. Bifascicular-block (LBBB or RBBB combined with anterior or left posterior fascicular block) or other intraventricular conduction abnormalities with a QRS duration $\geq$120 ms
6. Inadequate sinus bradycardia ($<$50 bpm) or sinoatrial block in absence of negative chronotropic medications or physical training
7. Pre-excited QRS complex
8. Prolonged or short QT interval
9. RBBB pattern with ST-elevation in leads V1–V3 (Brugada pattern)
10. Negative T wave in the right precordial leads, epsilon waves, and ventricular late potentials suggestive of ARVC
(3) Important comorbidities
1. Severe anemia
2. Electrolyte disturbance

LVEF, left ventricular ejection fraction; VT, ventricular tachycardia; SCD, sudden cardiac death; LBBB, left bundle branch block; RBBB, right bundle branch block; bpm, beats per minute; ARVC, arrhythmogenic right ventricular cardiomyopathy.

ILR implantation

We implanted the ILR (Medtronic Reveal DX®, Medtronic Inc., Minneapolis, MN, USA) subcutaneously in the left pectoral region. The ILR was able to save three manual activations of 7.5 min and automatic activations that were programmed as follows: (i) rapid ventricular tachycardia (RR interval <260 ms in at least 30 of 40 consecutive beats), (ii) ventricular tachycardia (RR interval 261–340 ms in 16 consecutive beats), (iii) pause (>3.0 s), and (iv) bradycardia (heart rate <30 min^{-1} in 4 consecutive beats).

Statistical analysis

The data were reported as the mean ± standard deviation. Continuous and categorical variables were compared by the means of a Student's *t*-test, Mann–Whitney test, or chi-squared test, as appropriate. The time from the definition of the unexplained syncope to the diagnosis or recurrent symptoms was described by means of Kaplan–Meier curves and compared with a log-rank test. A *p*-value <0.05 was considered statistically significant. JMP software version 10.0 was used for the analysis (SAS, Cary, NC, USA).

Results

Patient characteristics and diagnosis

The clinical characteristics are presented in Table 2. The patients with transient loss of consciousness (T-LOC) accounted for 5.9% (320 patients) of all the patients who were admitted into the cardiovascular internal medicine department of our hospital. In the initial and early evaluations, respectively, we could diagnose 208 and 201 patients with syncope, and non-syncope was diagnosed in 3 and 4 patients, respectively (Fig. 1). Reflex syncope was diagnosed in 29.1% of the cases, OH in 11.7%, and cardiac syncope in 34.0%. Unexplained syncope was diagnosed in 23.9% of the cases. Of the cardiac syncope patients, the number of patients in which the syncope was caused by bradycardia arrhythmias (15.9% of all syncope cases) was greater than that for tachycardia arrhythmias (9.9%), or structural heart disease (7.6%).

Syncope due to ischemic heart disease was diagnosed in 6.0% of the total syncope patients. In approximately half of the ischemic heart disease patients syncope was caused by vasospastic angina

Table 2
Patient characteristics.

N	547
Age (years)	60.4 ± 21.5
Male	328 (60.0%)
Hypertension	190 (34.7%)
Diabetes mellitus	60 (11.0%)
Injury	121 (22.1%)
Frequency of syncope (times)	2.1 ± 1.7
Admission	314 (57.4%)
Cardiac disease	261 (47.7%)
Congestive heart failure	19 (3.5%)
Ischemic heart disease	67 (12.2%)
OMI	35 (6.4%)
AP	17 (3.1%)
VSA	13 (2.4%)
Non ischemic heart disease	51 (9.3%)
CM	7 (1.3%)
HCM	13 (2.4%)
HHD	7 (1.3%)
Valvular cardiomyopathy	25 (4.6%)
Arrhythmia	151 (27.6%)
Brugada type ECG	19 (3.5%)
Long QT syndrome	5 (0.9%)
Bifascicular block	10 (1.8%)
SSS	7 (1.3%)
AVB	7 (1.3%)
Atrial fibrillation	94 (17.2%)
AFL	9 (1.6%)
PSVT	8 (1.2%)
VT	13 (2.4%)
Vf	2 (0.3%)

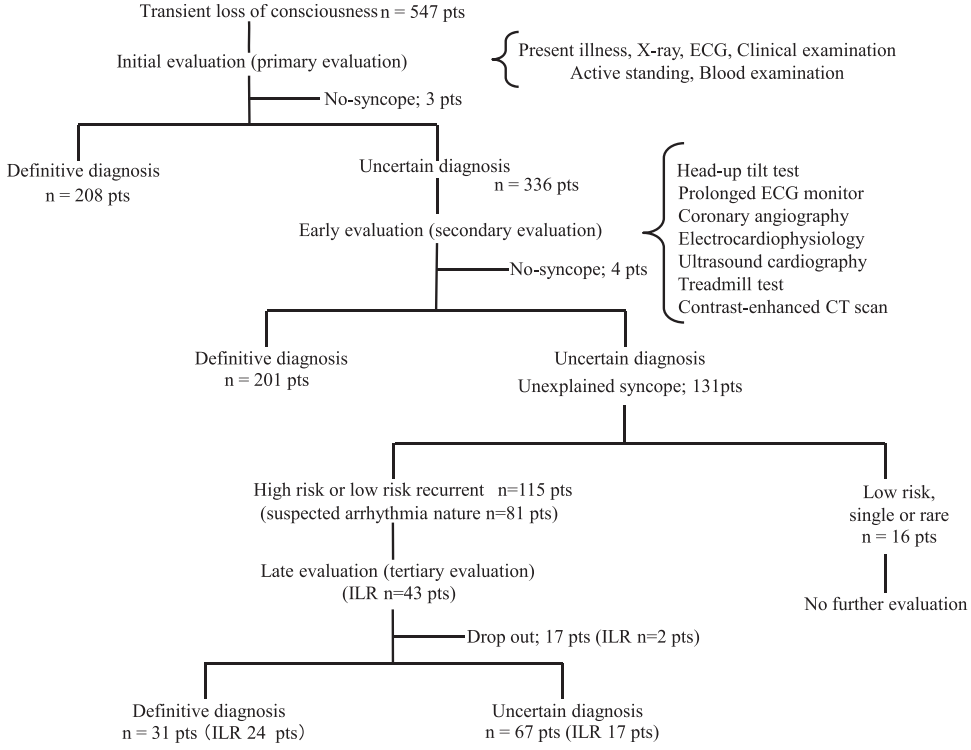

Fig. 1. Diagnostic flow chart of the results. Pts, patients; ECG, electrocardiogram; CT, computed tomography; ILR, implantable loop recorder.

Table 3A
Diagnostic results in the initial and early evaluations.

Syncope	Reflex syncope	Syncope due to OH	Cardiac syncope	Unexplained syncope
Total	159 (29.1%)	64 (11.7%)	186 (34.0%)	131 (23.9%)
Number	Vasovagal syncope 115 (21.0%)		Bradycardia 87 (15.9%)	Low risk 16 (2.9%)
	Situational syncope 35 (6.4%)		Tachycardia 54 (9.9%)	Low risk, recurrent 45 (8.2%)
	Carotid sinus syndrome 9 (1.6%)		Ischemic heart disease 33 (6.0%)	High risk 70 (12.8%)
			Non-ischemic heart disease 9 (1.6%)	
			Cardiovascular 3 (0.5%)	
Age (years)	★50.7 ± 22.3	61.0 ± 22.7	◆70.2 ± 15.5	58.1 ± 21.6

OH, orthostatic hypotension.
★ Reflex syncope vs. OH, cardiac syncope, unexplained ($p < 0.01$).
◆ Cardiac syncope vs. OH, reflex syncope, unexplained ($p < 0.01$).

(VSA). Of 17 VSA patients, 2 had an ECG documenting ventricular fibrillation with ST elevation after the syncope event.

Further, 22.4% and 84.4% of the non-cardiac syncope and cardiac syncope patients had cardiac disease, respectively, and 41.0% of the unexplained syncope patients had cardiac disease. The age of the cardiac syncope patients was significantly older than that of the others (Table 3A). For cardiac syncope, the age of the patients with bradycardia arrhythmias was the significantly highest cause of the cardiac syncope (bradycardia vs. tachycardia, and structural heart disease, 76.3 ± 10.9 years vs. 61.6 ± 19.0 years vs. 67.8 ± 13.2 years, respectively, $p < 0.0001$).

In the syncope patients with a definitive diagnosis in the initial and early evaluations, we analyzed what kind of assessment was essential to diagnose each syncopal episode. The most essential test in the initial evaluation was the medical history. The appropriate rate of the active stand test was only 2.9%. The diagnostic rate of the prolonged ECG tests (including the 24 hours Holter ECG and prolonged monitoring) was 18.2%. The diagnostic rates of EPS and CAG were 23.7% and 31.6%, respectively (Table 3B).

Comparison between the patients with a definitive diagnosis in the initial and early evaluations

The patient characteristics did not significantly differ between the initial and early evaluations. It was possible to diagnose the number of patients with reflex syncope in both evaluations, and it did not differ significantly. However, the numbers of situational syncope and OH patients in the initial evaluation were significantly greater than that in the early evaluation. The number of cardiac syncope patients in the early evaluation was significantly greater than that in the initial evaluation. The results were strongly associated with sick sinus syndrome and non-ischemic heart disease (Table 3C).

Unexplained syncope patients

One hundred thirty-one patients in whom a diagnosis could not be made in either evaluation were diagnosed with unexplained syncope. Of those 131 patients, there were

Table 3B
Diagnostic tests that established the cause of syncope in the initial and early evaluation.

Diagnostic test	Appropriate	Diagnostic yield
Medical history/physical examination	547 (100%)	134 (24.5%)
ECG on consultation (including in the ambulance)	547 (100%)	79 (14.4%)
Active standing test	16 (2.9%)	8 (50.0%)
Prolonged ECG monitoring	308 (56.3%)	56 (18.2%)
24 hours Holter ECG	286 (52.3%)	31 (10.8%)
Monitoring during admission	201 (36.7%)	17 (8.5%)
External loop recorder	23 (4.2%)	3 (13.0%)
Event monitoring in the cardiac device	8 (1.5%)	5 (62.5%)
Head-up tilt test (including CS massage)	232 (42.4%)	91 (39.2%)
CAG (including Ach stress test)	57 (10.4%)	18 (31.6%)
Electrophysiological test	76 (13.9%)	18 (23.7%)
Ultrasound cardiography	300 (54.8%)	9 (3.0%)
Contrast-enhanced CT scan	4 (0.7%)	3 (75.0%)
Treadmill test	53 (9.7%)	2 (3.8%)

ECG, electrocardiogram; CAG, coronary angiography; CT, computed tomography; CS, carotid sinus.

Table 3C
Comparison of the syncope patients in the initial and early evaluation.

Definitive diagnosis	Initial evaluation	Early evaluation	*p*-value
Patient characteristics			
N	208	201	NS
Age (years)	61.6 ± 21.9	60.6 ± 21.0	NS
Male	120 (57.7%)	117 (57.9%)	NS
Female	88 (42.3%)	85 (42.1%)	NS
Hypertension	71 (34.1%)	69 (34.2%)	NS
Diabetes mellitus	28 (13.5%)	21 (10.4%)	NS
Cardiac disease	108 (51.9%)	99 (49.0%)	NS
Congestive heart failure	8 (3.8%)	5 (2.5%)	NS
Ischemic heart disease	23 (11.1%)	27 (13.4%)	NS
Non ischemic cardiomyopathy	22 (10.6%)	18 (8.9%)	NS
Arrhythmia	56 (26.9%)	67 (33.2%)	NS
Diagnosis			
Reflex syncope	88 (42.3%)	71 (35.3%)	NS
Vasovagal syncope	56 (26.9%)	59 (29.3%)	NS
Situational syncope	32 (15.4%)	3 (1.5%)	<0.0001
Carotid sinus syndrome	0 (0.0%)	9 (4.5%)	<0.001
Syncope due to OH	41 (19.7%)	23 (11.4%)	<0.05
Cardiovascular syncope	79 (37.9%)	107 (53.2%)	<0.01
Bradycardia	37 (17.8%)	50 (24.9%)	NS
Sick sinus syndrome	16 (7.7%)	36 (17.9%)	<0.001
Atrioventricular block	18 (8.7%)	9 (4.5%)	NS
Bradycardia atrial fibrillation	3 (1.4%)	5 (2.5%)	NS
Tachycardia	26 (12.5%)	28 (13.9%)	NS
Supraventricular	5 (2.4%)	8 (4.0%)	NS
Ventricular	21 (10.1%)	20 (10.0%)	NS
Structural heart disease	16 (7.7%)	26 (12.9%)	<0.05
Ischemic heart disease	16 (7.7%)	17 (8.5%)	NS
Non-ischemic heart disease	0 (0.0%)	9 (4.5%)	<0.01
Vascular disease	0 (0.0%)	3 (1.5%)	NS

OH, orthostatic hypotension.

16 low-risk group patients. We finished evaluating the follow-up in the low risk-group at that point. There were 115 patients in the low-risk recurrent or high-risk groups. Of those 115 patients with unexplained syncope, 81 with a suspected arrhythmia were diagnosed to have an indication for an ILR implant. Forty-three (53.1%) of them consented to an ILR implantation. In particular, in the lone high-risk group, the proportion of patients was 46.0%. Seventeen patients were excluded because of incomplete follow-up data (2 patients with an ILR implantation). We followed up and compared the diagnostic rates between the 41 patients with an implanted ILR and 57 that underwent the conventional tests for the late evaluation during the observation period. The patient characteristics in both groups were not significant except for the admission to a hospital (Table 4A).

The median follow-up was 18 months from the definition of unexplained syncope. There were no death events in the unexplained syncope patients during the observation period. Of those 41 unexplained patients with implanted ILRs, syncope was diagnosed in 24 using the ILR. The estimated diagnostic rates were 47% and 65% at 1 and 2 years, respectively. Ten cardiac syncope patients, 10 non-cardiac syncope patients, and 4 non-syncope patients were diagnosed (Table 4B). Of 55 unexplained patients using conventional tests, 7 were diagnosed. The estimated diagnostic rates were 14% at 1 and 2 years. Five cardiac syncope patients, and 2 non-cardiac syncope patients were diagnosed (Table 4B). Although the symptom-free rate between those implanted with ILRs and those that underwent conventional tests was approximately the same, the estimated diagnostic rate in those implanted with ILRs was significantly greater than in those that underwent conventional tests (Fig. 2A and B). The recurrent symptom-free rate in the unexplained syncope patients was 50% at 1 year, however the recurrent symptom-free rate in the unexplained syncope patients that could be diagnosed and treated was 92.7% at 1 year (Fig. 3). Those 2 patients with recurrent symptoms after therapy were diagnosed with a recurrence of reflex syncope and OH.

Final diagnosis

The percentages of final diagnoses during each evaluation (initial, early, and late) are shown in Table 5. We were finally able to diagnose 81.7% of all T-LOC patients after all evaluations. Of 336 patients that could not be diagnosed in the initial evaluation, 236 patients (70.2%) were able to be diagnosed with syncope in the early and late evaluations. The numbers of cardiac syncope patients and non-cardiac syncope patients were 104 (31%) and 122 (36%), respectively (Table 5).

Table 4A
Comparison of the characteristics between the use of an ILR and the conventional group.

Unexplained syncope	ILR	Conventional	*p*-value
N	41	57	NS
Age (years)	59.5 ± 20.5	60.4 ± 22.6	NS
Male	26 (63.4%)	35 (61.4%)	NS
Hypertension	15 (36.6%)	22 (38.6%)	NS
Diabetes mellitus	4 (9.8%)	7 (12.3%)	NS
Cardiac disease	21 (51.2%)	24 (42.1%)	NS
Arrhythmia	10 (24.4%)	17 (29.8%)	NS
Frequency of syncope (times)	2.4 ± 0.2	2.1 ± 0.2	NS
Admission (%)	41 (100%)	26 (45.6%)	<0.0001
Injury (%)	19 (46.3%)	16 (28.1%)	NS

ILR, implantable loop recorder.

Table 4B
Diagnoses achieved in the late evaluation.

Diagnosis	ILR	Conventional	Total (% of diagnosed patients)
Bradycardia	8	2	10 (32%)
Supraventricular tachycardia	2	2	4 (13%)
Ventricular tachycardia	0	1	1 (3%)
Sinus rhythm			
Reflex or OH	10	0	10 (32%)
Epilepsy	4	2	6 (19%)
Total	24	7	31 (100%)

ILR, implantable loop recorder; OH, orthostatic hypotension.

Discussion

In this retrospective study of 547 patients, the major findings were as follows: (1) Most of our cardiac syncope patients had cardiac disease, similar to those in Western countries. (2) The initial evaluation during the first medical examination was important for diagnosing OH and situational syncope. (3) VSA was an important cause of cardiac syncope and a CAG with an acetylcholine stress test was used for the diagnosis. (4) The proportion of unexplained patients with a suspected arrhythmia

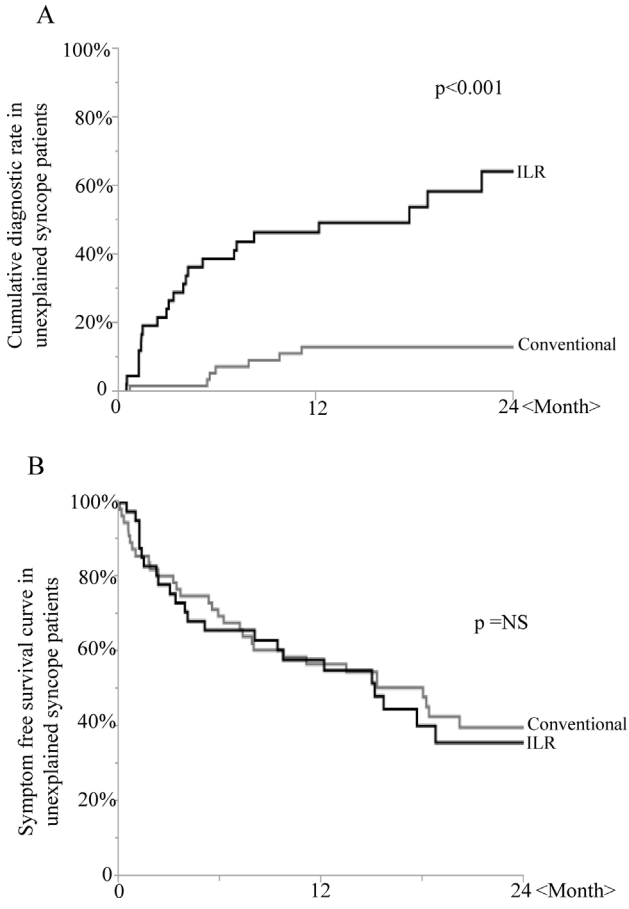

Fig. 2. (A) Cumulative diagnostic rates between the use of an ILR and conventional tests. (B) Symptom-free survival curve for the use of an ILR and conventional tests. Although the symptom-free rate between the group implanted with ILRs and the conventional test group was approximately the same, the estimated diagnostic rate in the group implanted with the ILRs was significantly greater than that in those that underwent conventional tests. ILR, implantable loop recorder.

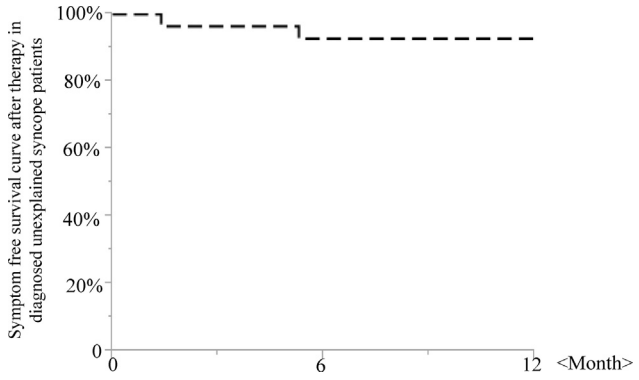

Fig. 3. Symptom-free survival curve after the therapy in patients with diagnosed unexplained syncope. The proportion of patients free of recurrent symptoms was 92.7% at 1 year after the therapy in patients with diagnosed unexplained syncope.

nature that consented to an ILR implantation was low. (5) An ILR was useful for diagnosing unexplained syncope, and the amount of recurrent symptoms was greatly reduced in the patients with unexplained syncope that could be diagnosed and treated.

To the best of our knowledge there have been no previous reports showing the present circumstances of syncope in Japanese hospitals. We showed the cause of syncope involved in cardiovascular internal medicine. Four hundred-ten syncope patients were diagnosed in the initial and early evaluations, and the most frequent cause of syncope was cardiac causes. It is known that cardiac causes of syncope are more frequently observed in elderly patients than in young patients and conversely, reflex syncope is more frequent in young patients [9]. Our data for the age distribution when cardiac syncope presented showed that it was more frequently due to bradycardia arrhythmias in elderly patients.

Alboni et al. previously reported that 95% of cardiac syncope patients had cardiac disease. Thus, they mentioned that the presence of suspected or certain heart diseases is a strong predictor of a cardiac cause of syncope [10]. Most of our cardiac syncope patients had cardiac disease, similarly to their report. However, 41% of the unexplained syncope patients had cardiac disease. We think that these patients must be carefully followed up.

We were able to diagnose 38.5% of all the T-LOC patients in the initial evaluation. A previous report [11,12] showed that the initial evaluation was able to define the cause of syncope in 23–50% of the patients. These findings in the clinical history, physical examination, or ECG have an important role in diagnosing syncope. In particular, the initial evaluation was important for diagnosing OH and situational syncope. The representative test for diagnosing reflex syncope is the HUT, which is not known to be useful for situational syncope [13,14]. It may not be possible to diagnose OH by an active standing test according to the conditions at that time (i.e. improvement in dehydration and withdrawal of the causative drug). We may not be able to diagnose syncope if we neglect the initial evaluation.

The diagnostic rate of a prolonged ECG required for a definitive diagnosis of syncope was 18.2% for both evaluations. Most of the patients had cardiac syncope. Croci et al. reported that 16% of syncope was diagnosed by prolonged ECGs in the syncope unit, and the proportion diagnosed by an EPS was low [12]. Our study also showed that the diagnosis of syncope by an invasive EPS was low. A CAG is not generally included in the diagnostic testing for syncope in Western countries [12]. The CAG was able to diagnose most patients with syncope due to VSA without coronary artery stenosis. The diagnostic method was to infuse acetylcholine into the coronary artery [15]. Abe et al. reported that VSA is not rare in Japan and east Asia [16]. VSA is known to induce arrhythmias [17,18] and failure of the cardiac pump function [19] causing syncope. In particular, VSA is often the cause of sudden cardiac death due to ventricular arrhythmias [18]. Two VSA patients were clinically documented with ventricular fibrillation and ST elevation after a syncopal event in the present study. Therefore, VSA is an important illness involved in cardiac syncope in Japan.

We could not diagnose syncope in 23.9% of all the patients until the initial and early evaluations. There were 115 low-risk recurrent and high-risk patients. ILRs have been approved for use in Japan since 2009. The present study started from that same year. The consent rate for an implantation of an ILR was 53.1%. It is well known that ILRs are useful devices for diagnosing unexplained syncope [3–6]. However, we obtained consent from only half of the appropriate risk patients. To the best of our knowledge this is the first report regarding the consent rate for an ILR in Japan. Farwell et al. reported the diagnostic efficacy comparison of 201 unexplained syncope patients between ILRs and conventional tests in a prospectively randomized trial [4]. Only 2 unexplained syncope patients refused the study. Brignole et al. reported that only 6% of the suspected reflex syncope patients refused to have an ILR implanted for a diagnostic observation [20]. The consent rates

Table 5
The percentage of final diagnoses during each evaluation (initial, early, and late).

Etiology of syncope	Initial evaluation (n = 547)	Early evaluation (n = 336)	Late evaluation (n = 98)	Final diagnosis (n = 547)
Diagnostic rate	211 (38.5%)	205 (61.0%)	31 (31.6%)	447 (81.7%)
Vasovagal	56 (10.2%)	59 (17.6%)	7 (7.1%)	123 (22.5%)
Situational	32 (5.85%)	3 (0.9%)	1 (1.0%)	35 (6.4%)
Carotid sinus syndrome	–	9 (2.7%)	–	9 (1.6%)
Syncope due to OH	41 (7.5%)	23 (6.8%)	2 (2.0%)	66 (12.1%)
Non-cardiac syncope	129 (23.6%)	94 (28.0)%	10 (10.2%)	233 (42.6%)
Sick sinus syndrome	16 (2.9%)	36 (10.7%)	6 (6.1%)	58 (10.6%)
Atrioventricular block	18 (3.3%)	9 (2.7%)	4 (4.1%)	31 (5.7%)
Bradycardia atrial fibrillation	3 (0.5%)	5 (1.5%)	–	8 (1.5%)
Supraventricular tachycardia	5 (0.9%)	8 (2.4%)	4 (4.1%)	17 (3.1%)
Ventricular tachycardia	21 (3.8%)	20 (6.0%)	1 (1.0%)	42 (7.7%)
Ischemic heart disease	16 (2.9%)	17 (5.1%)	–	33 (6.0%)
Non-ischemic heart disease	–	9 (2.7%)	–	9 (1.6%)
Vascular disease	–	3 (0.9%)	–	3 (0.5%)
Cardiac syncope	79 (14.4%)	107 (31.8%)	15 (15.3%)	201 (36.7%)
No-syncope	3 (0.5%)	4 (1.2%)	6 (6.1%)	13 (2.4%)

OH, orthostatic hypotension.

appear to be lower in the present study. In clinical practice we must enlighten the unexplained syncope patients to the importance of diagnosing syncope with ILRs.

ILRs were useful devices for diagnosing syncope in the present study. The annual cumulative diagnostic rate was calculated to be 43–50% over a maximum follow-up of 2 years in previous Western reports. The diagnostic rate increased rapidly during the six months period after the ILR implantation, and was followed by a linear increase in the subsequent period [4–6]. Their finding of the diagnostic rate was consistent with our pattern of the diagnostic rate. In contrast, a diagnosis could be achieved in only 7 (13%) unexplained syncope patients that underwent conventional tests. The curve in the diagnostic rate exhibited a concentrated increase from 6 months to 12 months after the late evaluation was begun, and we could not diagnose those patients at all after 12 months even though recurrent symptoms had developed. It may be difficult to diagnose unexplained syncope without using an ILR. However, in the case that unexplained syncope patients could be diagnosed and treated, the symptom recurrence was greatly reduced.

There were no death events in the unexplained syncope patients during the observation period. An ILR is not a treatment device but a diagnostic device. We should carefully pay attention when selecting between the conventional method, an ILR, and cardiac device therapies such as pacemakers and implantable cardiac defibrillators [21], in order to avoid cardiac death events.

We were finally able to diagnose 81.7% of all T-LOC patients in the present study. Of 336 patients that could not be diagnosed in the initial evaluation, 236 (70.2%) patients could be diagnosed in the early and late evaluations, and the numbers of cardiac syncope and non-cardiac syncope patients that could be diagnosed was about equal. Also, the number of cardiac syncope patients that were diagnosed in the early evaluation was greater than that in the initial evaluation. In cases with unexplained syncope in the initial evaluation, the primary physicians should perform further tests for more advanced evaluation. However, if the consent rate for ILR in unexplained syncope patients with appropriate risk in the late evaluation is high, the diagnostic rate might be higher.

Limitations

Our data were based on a follow-up analysis in the division of cardiology at a single Japanese university hospital. Reflex syncope is generally the most frequent type of syncope in Western countries [9,22,23]. The prevalence of the causes of syncope differs depending on the clinical setting, age of the patients, and diagnostic definitions, making a comparison between different studies difficult [8]. Our data appear to have a patient selection bias because some of the patients included were referral patients from neighboring clinics and other medical institutions. Therefore, all patients consist of a suspected cardiogenic syncope population. In particular, the incidence of reflex syncope and OH appear to be limited only in the cardiology department. However we have to diagnose and choose the appropriate treatment for those syncope patients. It appears worthwhile to determine the facts of the syncope in Japanese hospitals.

Conclusions

Syncope is induced by various causes. It is important that we understand the characteristics of each cause of syncope. The ILR helped to effectively determine the diagnosis for unexplained syncope. The consent rate for an ILR implantation for appropriate unexplained syncope was low. The recurrent symptoms in the patients in whom unexplained syncope could be diagnosed and treated were greatly reduced. We therefore need to educate the patients at risk with unexplained syncope about the importance of making a diagnosis of syncope.

Conflict of interest

There are no conflicts of interest or financial disclosures to declare regarding our manuscript.

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